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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with endrin. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1979a. Reviews of the Environmental Effects of Pollutants: III. Endrin. Prepared by the Health Effects Research Laboratory, Cincinnati, OH. EPA-600/1-79-005. NTIS ORNL/EIS-131.

U.S. EPA. 1980a. Ambient Water Quality Criteria for Endrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-047. NTIS PB 81-117582.

U.S. EPA. 1980b. Hazard Profile for Endrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1985a. Drinking Water Criteria Document for Endrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA/600/X-84/176. NTIS PB86-117967.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime

exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

There were several chronic and subchronic oral toxicity studies with endrin available. Data obtained from studies using dogs appeared to permit best estimation of thresholds of toxicity, and therefore RfD_{SO} and RfD_{O} values were calculated from dog studies. The RfD_{SO} was based on a NOAEL of 1 ppm in the diet (0.045 mg/kg/day) from an 18-month study in which higher doses (3 ppm) caused increased relative organ weights, and still higher doses (5.50 ppm) caused mortality (Treon et al., 1955). The RfD_{O} was based on a NOAEL of 1 ppm in the diet (0.025 mg/kg/day) from a 2-year study in which higher doses (2 ppm) caused mild histopathological changes in the liver (CBI, 1986; U.S. EPA, 1985b). An uncertainty factor of 100 was applied to these NOAELs to derive an RfD_{SO} of 0.00045 mg/kg/day (0.03 mg/day for a 70 kg human) and an RfD_{O} of 0.00025 mg/kg/day (0.02 mg/day). A maximum CS of 52 was calculated using data from a 2-year mouse study in which 2.5 ppm in the diet caused decreased survival (Reuber, 1979).

The available data were inadequate for calculation of RfD_{SI} and RfD_{I} values.

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LIST OF ABBREVIATIONS

AADI	Adjusted acceptable daily intake
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EEG	Eletroencephalogram
HA	Health advisory
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and half-lives of endrin are presented in Table 1-1.

In the atmosphere, endirin is likely to be present primarily adsorbed onto airborne particulate matter. Atmospheric transport of endrin exceeds any other mechanism and is considered to be primarily responsible for world-wide dissemination of this pesticide. The primary method of removal from the atmosphere is by particle fall-out or precipitation washout (U.S. EPA, 1979a). In water, volatilization and co-distillation reallocate endrin to the atmosphere and dissipation occurs as a result of biochemical and photo-chemical degradation. Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms are significant fate processes (U.S. EPA, 1979a). In soil, endrin is removed by volatilization, leaching into groundwater, wind erosion, surface water translocation, photodecomposition and microbial degradation. Endrin removal by microbial degradation, however, is contingent upon the presence of the appropriate microbial species and favorable soil conditions. Half-lives ranging from 1 day to 11.3 years have been observed, depending upon a wide variety of factors including soil properties, agricultural processes, topology and weather conditions (U.S. EPA, 1979a).

The half-lives of endrin in air and water could not be located in the available literature.

TABLE 1-1

Selected Chemical and Physical Properties and Half-lives for Endrin

Property	Value	Reference
CAS number:	72-20-8	
Chemical class:	halogenated cyclodiene	
Molecular weight:	380.93	U.S. EPA, 1985a
Vapor pressure: (technical grade)	2.7×10^{-7} mm Hg at 25°	U.S. EPA, 1985a
Water solubility:	0.23 mg/ℓ at 25°C	U.S. EPA, 1985a
Log octanol/water partition coefficient:	5.34	U.S. EPA, 1985a
Biocentration factor:	140-222, alga (mixed species); 3000, mussels (mixed species); 7000-10,000, fathead minnow (Pimephales promelas); 2500-6400, sheepshead minnow (Cyprinodon variegatus)	U.S. EPA, 1980a
Soil adsorption coefficient:	9800-19,100 (estimated)	Lyman et al., 1982
Half-lives:		
Air and water	NA	
Soil	1 day to 11.8 years (depending upon existing soil conditions)	U.S. EPA, 1979a

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The presence of detectable endrin residues in wildlife and livestock exposed to endrin-contaminated food indicates that endrin is absorbed from the gastrointestinal tract (U.S. EPA, 1985a). No quantitative estimates of absorption were presented, however. Studies summarized by IARC (1974), indicated that endrin when administered orally to rats is absorbed from the gastrointestinal tract, but no estimates of absorption were provided.

In a study of the metabolic fate of endrin in rabbits, Bedford et al. (1975) reported that rabbits excreted ~50% of an oral dose of radiolabeled endrin in the urine, suggesting that at least that much was absorbed from the gastrointestinal tract. For comparison, the authors reported that rats excreted ~2% of an oral dose in the urine. IARC (1974) reported that rats excreted <1% of an oral endrin dose in the urine.

2.2. INHALATION

No quantitative data regarding inhalation absorption of endrin were located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Some of the more relevant subchronic oral toxicity studies with endrin are summarized in Table 3-1.

Nelson et al. (1956) fed groups of five male and five female Sprague-Dawley rats diets containing 0, 1, 5, 25, 50 or 100 ppm endrin for 16 weeks. All high-dose rats died in the first 2 weeks. All treated rats lost weight and were hypersensitive to various stimuli. Paired feeding experiments indicated that the body weight losses were not caused by reduced food consumption alone. Convulsions occurred only in rats at the three higher dose levels.

Treon et al. (1955) fed Carworth rats (6/sex/group) 0, 1, 2 or 5 mg/kg/day endrin, 5 days/week for 10 weeks. Female rats regardless of age (3 were 29 days and 3 were 6 months of age at the initiation of the experiment) appeared to be more susceptible than males to the cumulative action of endrin. Mortality occurred in 2/5 females but no deaths occurred in males at the 2 mg/kg/day dose level. However, 3/3 males died following 5 days of oral administration of endrin at 5 mg/kg/day. All treated animals developed hypersensitivity to stimuli and weight loss but generally male rats were less affected than female rats.

In a second experiment, Treon et al. (1955) orally administered endrin at 0 or 1 mg/kg/day for 5 days/week to female rats (5/group). These rabbits lost weight and developed abdominal distension; 4/5 rabbits died over the 10-week period.

TABLE 3-1

Summary of Subchronic Oral Toxicity Data For Endrin

Species/Strain	No./Sex/Group	Dose	Duration	Effect	Reference
Rats/Sprague-Dawley	5/sex/group	0, 1, 5, 25, 50 or 100 ppm diet	16 weeks	Dose-related signs of toxicity at 25-100 ppm including mortality, convulsions, reduced body weights; hypersensitivity to stimuli and decreased body weights in all treated rats	Nelson et al., 1956
Rats/Carworth	3-6/sex/group	0, 1, 2 or 5 mg/kg/day, 5 days/week	10 weeks	2/6 females died at 2 mg/kg/day; 3/3 males died at 5 mg/kg/day; no deaths at 1 mg/kg/day	Treon et al., 1955
Rats/Osborne-Mendel	5/sex/group	0, 2.5-80 ppm diet for 6 weeks	8 weeks	Some mortality at $\geq$20 ppm; no effects on body weight at $\leq$10 ppm	NCI, 1979
Rats/Sprague-Dawley	20-50/NR/group	0, 0.8, 1.7, 3.5 mg/kg/day, 5 days/week for 7 months	7 months	Convulsions and mortality in high-dose rats; others susceptible to convulsions when exposed to auditory stimuli	Speck and Maaske, 1958
Mice/B6C3F1	5/sex/group	0, 2.5, 5, 10, 20 ppm diet for 6 weeks	8 weeks	Some mortality at 10 ppm; no mortality or body weight effects at 5 ppm	NCI, 1979
Squirrel monkeys/NR	NR	0.2 mg/kg/day in diet	NR	Altered EEG pattern after 7 days	Revzin, 1968
Rabbits/NR	5 females	1 mg/kg/day, 5 days/week	10 weeks	4/5 died	Treon et al., 1955

NR = Not reported

Feeding studies were conducted to estimate the maximum tolerated doses of endrin in Osborne-Mendel rats and B6C3F1 mice for a National Cancer Institute study of carcinogenicity (NCI, 1979). Five males and five females were given food with or without endrin for 6 weeks, followed by observation for 2 weeks.

For rats, endrin was added to the feed in 2-fold increasing concentrations, ranging from 2.5-80 ppm (NCI, 1979). There were no deaths at 10 ppm and mean weight gains were not different from controls. At 20 ppm, one animal of each sex died, but weights of survivors were not significantly affected. Thus, the maximum subacute tolerated dose was ~15 ppm.

In the same 1979 NCI subchronic study, mice were given feed containing from 2.5-20 ppm endrin. At 10 ppm, 3 males and 4 females died in the group of 10 mice. No mortality occurred in the 5 ppm group; mean weight gains were comparable with that of controls. The maximum subchronic tolerated dose was thus ~5 ppm. In these subchronic exposures, increased mortality was the only toxic effect reported other than hyperexcitability in male mice receiving >5 mg/kg diet.

Revzin (1968) monitored EEG patterns in squirrel monkeys that received 0.2 mg/kg/day endrin in the diet. Changes in the EEG pattern were apparent after 7 days of dosing at this level.

3.1.2. Inhalation. Treon et al. (1955) conducted subchronic inhalation experiments with several species exposed to endrin vapors at 5.44 mg/m^3 (0.36 ppm) 7 hours/day, 5 days/week for a total of 130 exposure days over a 185-day period. The following mortalities occurred: cat 0/1, guinea pigs 0/2, hamsters 0/2, rats 0/3, rabbits 2/4 and mice 1/3. The authors stated that tissues were normal in most of the surviving animals, except that rabbits had developed a granulomatous type of pneumonitis.

3.2. CHRONIC

3.2.1. Oral. The available data from long-term oral bioassays are presented in Table 3-2; however, the primary focus of many of these studies was carcinogenicity, and therefore they will be discussed in greater detail in Section 4.2.

Treon et al. (1955) fed groups of 20 male and 20 female Carworth rats diets containing 0, 1, 5, 25, 50 or 100 ppm endrin for 2 years. Rats receiving 50 or 100 ppm exhibited hypersensitivity to external stimuli, occasional convulsions and liver degeneration. In addition, after 80 weeks of treatment, increased mortality in rats was noted at 25, 50 and 100 ppm in males and at 50 and 100 ppm in females. Effects on body weight were reported at 20 and 40 weeks. Females at 5 and 25 ppm appeared to have a greater rate of body weight gain than controls, while body weights in males appeared to be slightly depressed at these levels. At $\geq$50 ppm, rats of both sexes appeared to have a slightly increased rate of body weight gain, but since mortality was high in these groups, the survivors may have been the larger rats. Males at 5 and 25 ppm had increased relative liver weights compared with controls, while rats at 1 ppm were not different from controls.

Treon et al. (1955) also conducted a study with beagle dogs in which groups of 1-4 were fed diets containing 0-50 ppm endrin for up to 18 months. All dogs fed 10-50 ppm (0.49-4.00 mg/kg/day) died, and >50% of those fed 5-8 ppm (0.20-0.65 mg/kg/day) died. Actual endrin intakes were reported by the authors. All dogs receiving $\leq$4 ppm (0.15-0.21 mg/kg/day) survived, but growth was affected in the 4 ppm groups. The 3 ppm (0.12-0.25 mg/kg/day) group had significantly higher relative kidney and heart weights than controls. Dogs fed 1 ppm endrin were similar to controls in all parameters,

TABLE 3-2

Summary of Data from Endrin Carcinogenicity/Chronic Toxicity Studies

Species/Strain	Number/Sex/Group	Dose/Duration	Length of Study	Compound Purity	Effects	Reference
Rats/Osborne-Mendel	50/sex/group (10/sex/matched control; 50/sex/pooled controls)	0, 3 or 6 ppm diet for females, 0, 2.5, 5 ppm diet for males for 110-114 weeks	110-114 weeks	technical	Clinical signs of toxicity (e.g., hyperexcitability) in all treated groups	NCI, 1979
Rats/Carworth	20/sex/group	0, 1, 5, 25, 50 or 100 ppm diet for 2 years	2 years	NR	Clinical signs of toxicity and increased mortality in the two higher dose groups; increased relative liver weights in males at 5 and 25 ppm; no effects on rats fed 1 ppm	Treon et al., 1955
Rats/Osborne-Mendel	50/sex/group	0, 2, 6, 12 ppm for 2 years	2 years	technical, 98%	Increased incidence of cloudy swelling in the liver and renal tubular epithelium, increased incidence of congestion and focal hemorrhages in the lungs in treated rats, but none of these were dose-related.	Deichmann et al., 1970
Rats/Osborne-Mendel	24/sex/group	0, 0.1, 1.0, 5, 10, 25 ppm diet for 104 weeks	104 weeks	99%	Because of high initial mortality of high-dose rats, this group was restarted using slightly older rats; higher incidence of renal disease in treated male rats, but not dose-related; threshold appeared to be 1 ppm	Reuber, 1978
Mice/B6C3F1	50/sex/group (10/sex/matched control, 50/sex/pooled controls)	0, 1.6 or 3.2 ppm diet (males) 0, 2.5 or 5 ppm diet (females) for 80 weeks	90-91 weeks	technical	Clinical signs of toxicity (e.g., hyperexcitability) in all treated groups; decreased survival of high-dose males	NCI, 1979
Mice/C3HF	50/sex/group (75/sex/group for controls)	0 or 2.5 ppm diet for 104 weeks	104 weeks	NR	Decreased survival of treated mice	Reuber, 1979
Mice/C57B1/6J or C3B2F1/J	100/NR/group	0, 0.3 or 3.0 ppm diet for 78-104 weeks	78-104 weeks	99%	Some convulsions occurred initially in high-dose mice.	Reuber, 1979

Species/Strain	Number/Sex/Group	Dose/Duration	Length of Study	Compound Purity	Effects	Reference
Dogs/beigle	10 males and 5 females, 4-6/ group	0, 1 or 5 ppm diet (0, 0.025 or 0.125 mg/day) for up to 2 years	2 years	NR	Treated dogs had higher incidence of hyperplasia in various organs than controls	Reuber, 1979
Dogs/beagle	1-4/NR/group	0-50 ppm diet for up to 18 months	18 months	NR	All dogs fed 10-50 ppm (0.49-5 mg/kg/day) died; some mortality in groups fed 5-8 ppm, growth was affected at 4 ppm (0.15-0.21 mg/kg/day), increased relative kidney and heart weights at 3 ppm (0.12-0.25 mg/kgday); no adverse effects, including histopathological effects, in two females and two males fed 1 ppm (0.045-0.120 mg/kg/day)	Treon et al., 1955

NR = Not reported

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including gross pathology and histopathology. According to the authors, the dogs (two males and two females) on the 1 ppm diet actually consumed 0.045-0.120 mg/kg/day.

3.2.2. Inhalation. U.S. EPA (1985a) summarized several studies of humans occupationally exposed to organochlorine insecticides including endrin. Wolfe et al. (1963) reported that no illnesses were found in agricultural workers exposed to calculated dermal exposures of 2 or 0.28 mg/kg/day and respiratory exposures of 0.044 or 0.0011 mg/kg/day on two separate occasions. Jager (1970) monitored workers in a pesticide manufacturing plant in the Netherlands and found that blood endrin levels of 0.05-0.20 µg/mL were associated with signs of intoxication. In studying 233 workers exposed to endrin for 4-13.3 years, Jager (1970) found no abnormalities in illnesses, clinical chemistry parameters or EEG readings. Some induction of hydroxylating enzymes had occurred in some of these workers, but they showed no signs of toxic effects. Hoogendam et al. (1962) also noted EEG disturbances in some workers that had been exposed to endrin.

Treon et al. (1955) reported the effects of inhalation exposure of a number of species including rats, rabbits, mice, cats and hamsters to "vapors" of endrin. Animals were exposed to 0.36 ppm (5.62 mg/m³) endrin vapors for 7 hours/day, 5 days/week for 185 days. Mortality occurred in 1/3 mice and 2/4 rabbits; no other deaths were reported. Pathological findings were similar to those observed for other routes of administration, i.e., weight loss and hypersensitivity.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The U.S. EPA (1980a) reviewed some early studies that indicated that endrin was teratogenic in mice and hamsters. Generally, single oral doses of relatively large magnitude (5 mg/kg) were used, far above those associated with chronic toxicity.

More recent studies (Table 3-3) indicate that endrin does not produce teratogenic effects in rats and that effects on the fetuses of mice and hamsters occur only at levels associated with chronic toxicity. Kavlock et al. (1981) treated CD rats with endrin at 0.075, 0.150, 0.300 or 0.450 mg/kg/day on days 7-20 of gestation. CD-1 mice were treated with 0.5, 1.0, 1.5 or 2.0 mg/kg/day on gestation days 7-17. Endrin was dissolved in corn oil and administered by gavage; vehicle controls were also maintained. Pregnant rats and mice were necropsied on gestation days 21 and 18, respectively. In rats, a marked reduction in maternal body weight gain occurred at 0.300 and 0.450 mg/kg/day. There were no effects on relative liver weights, fetal implants, mortality, fetal body weights and the incidences of skeletal or visceral anomalies. In mice, a dose-related increase in maternal mortality was observed at 1.5 and 2.0 mg/kg/day. Maternal body weight gain was reduced in a dose-related manner at $\geq$1.0 mg/kg/day and a dose-related increase in relative liver weight was noted in all treated groups. A dose-related decrease in fetal body weights and retardation of skeletal development were also observed at $\geq$1.0 mg/kg/day.

Chernoff et al. (1979) treated Syrian golden hamsters with gavage doses of 0, 0.75, 1.5, 2.5 or 3.5 mg/kg/day on days 4-15 of gestation or doses $\leq$10 mg/kg on day 8 of gestation. Mortality and decreased maternal weight gain occurred at doses of $\geq$1.5 mg/kg/day. Increased fetal mortality, reduced fetal body weight, and retardation of skeletal development also occurred at these levels. No treatment-related maternal or fetal effects occurred at 0.75 mg/kg/day.

TABLE 3-3

Reproductive Effect Studies with Orally Administered Endrin*

Species/Strain	Concentration or Dosage	Route/Vehicle	Duration of Treatment	No. of Litters	Effects	Reference
Rats/CD	0.075 mg/kg/day	gastric intubation/corn oil	days 7-20 of gestation	14	No effect on maternal weight gain or fetus.	Kavlock et al., 1981
Rats/CD	0.150 mg/kg/day	gastric intubation/corn oil	days 7-20 of gestation	27	No effect on maternal weight gain or fetus.	Kavlock et al., 1981
Rats/CD	0.300 mg/kg/day	gastric intubation/ corn oil	days 7-20 of gestation	29	Significant decrease in maternal weight gain, no effect on fetus	Kavlock et al., 1981
Rats/CD	0.450 mg/kg/day	gastric intubation/corn oil	days 7-20 of gestation	12	87% decrease in maternal weight gain, no effect on fetus	Kavlock et al., 1981
Rats/CD	0.075 mg/kg/day 0.150 mg/kg/day 0.300 mg/kg/day	oral gavage/ corn oil	7-15 of lactation	13 13 5	No effect on pup survival or growth, mid- and high-dose pups were more active in mazes	Gray et al., 1981
Mice/CFW Swiss	5 ppm	diet	4 months before and during gestation	NR	Parental mortality, decreased litter size	Good and Ware, 1969
Rats/Sprague-Dawley	5 ppm	diet	60 days before and during gestations	NR	Increased resorptions	Green, 1969
Mice/CD-1	2.5 mg/kg/day	oral gavage/ corn oil	day 9 of gestation	10	Congenital abnormalities: open eye, cleft palate	Ottolenghi et al., 1974
Mice/CD-1	0.5 mg/kg/day	gastric intubation/corn oil	days 7-17 of gestation	31	Maternal liver enlargement	Kavlock et al., 1981
	1.0 mg/kg/day	gastric intubation/corn oil	days 7-17 of gestation	32	Reduced maternal weight gain; decreased fetal weight and skeletal and visceral maturation at $\geq$1.0 mg/kg/day.	Kavlock et al., 1981
Mice/CD-1	1.5 mg/kg/day	gastric intubation/corn oil	days 7-17 of gestation	12	Maternal lethality; no teratogenic or embryolethal effects; decreased pup weight gain and locomotor activity	Kavlock et al., 1981
	2.0 mg/kg/day (single dose)	gastric intubation/corn oil	days 7-17 of gestation	2	No dose-related evidence of open eyes and cleft palate; maternal mortality	Kavlock et al., 1981

TABLE 3-3 (cont.)

Species/Strain	Concentration or Dosage	Route/Vehicle	Duration of Treatment	No. of Litters	Effects	Reference
Mice/CD-1	2.0 mg/kg/day	gastric intubation/corn oil	days 8-12 of gestation	17	Reduced maternal weight and fetal weight	Chernoff and Kavlock, 1982
Mice/CD-1	2.0 mg/kg/day	gastric intubation/corn oil	days 14-18 of gestation	17	No effect on fetal weight or survival	Gray and Kavlock, 1984
Hamsters/ Syrian golden	5.0 mg/kg/day	oral gavage/ corn oil	day 7 of gestation; day 8 of gestation, day 9 of gestation	7 21 8	Fetal death, growth retardation, congenital abnormalities in 28% of fetuses treated on day 8: open eye 22%, webbed foot 16%, cleft palate 5%, fused ribs 8%	Ottolenghi et al., 1974
Hamsters/ Syrian golden	>0.75 mg/kg/day	oral gavage/ corn oil	days 4-15 of gestation	19	Maternal toxicity (tremors reduced weight gain, lethality) and fetal toxicity (mortality, reduced fetal weight, reduced skeletal ossification)	Chernoff et al., 1979
Hamsters/ Syrian golden	≥1.5 mg/kg/day	oral gavage/ corn oil	days 4-15 of gestation	21	Maternal lethality, weight reduction; meningoencephaloceles in fetuses of two litters	Chernoff et al., 1979
Hamsters/ Syrian golden	>1.5 mg/kg/day	oral gavage/ corn oil	day 8 of gestation	34	Meningoencephaloceles: no overt embryolethal or maternotoxic affects	Chernoff et al., 1979
Hamsters/ Syrian golden	≥5.0 mg/kg/day	oral gavage/ corn oil	day 8 of gestation	50	Fused ribs and meningoencephaloceles, no overt embryolethal or maternotoxic effects	Chernoff et al., 1979
Hamsters/ Syrian golden	0.75, 1.5 mg/kg/day	oral gavage/ corn oil	days 5-14 of gestation	13	Increased locomotor activity of offspring at 1.5 mg/kg/day	Gray et al., 1981
Deer mice (Peromyscus maniculatus asgoodi)/NA	2, 4 or 7 ppm	diet	intervals over a 7-month period	NR	Parental mortality, decreased survival of offspring	Morris, 1968

*Source: U.S. EPA, 1985a

NA = Not applicable; NR = not reported

In reviewing studies of the reproductive effects of dietary endrin, U.S. EPA (1985a) concluded that at high gavage doses endrin was teratogenic in mice and hamsters but not in rats. They also concluded that endrin given to pregnant animals was associated with behavioral changes in the offspring in all three species.

3.3.2. Inhalation. No data concerning possible reproductive or teratogenic effects of endrin from inhalation exposures were located in the available literature.

3.4. TOXICANT INTERACTIONS

There is relatively little information available concerning interaction of endrin with other pesticides. Keplinger and Deichmann (1967) studied acute oral toxicity of combinations of pesticides, and found that LD_{50} values were lower than expected (i.e., suggestive of some antagonistic effect) for mixtures of endrin with parathion, DDT or Delnav. Additive effects were indicated when endrin was administered with diazinon, toxaphene or malathion. Endrin plus aldrin showed a more than additive effect, and endrin plus chlordecone exerted a potentiating effect. Ludke (1976) reported that endrin was more toxic to birds if they already had a body burden of other organochlorine compounds.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding carcinogenicity of endrin in humans by oral exposure could not be located in the available literature.

4.1.2. Inhalation. Studies of workers occupationally exposed to endrin have not demonstrated any association between exposure and incidence of any type of cancer (IARC, 1974). Jager (1970) and Jager and Versteeg (1973) studied 233 workers employed in the manufacture of endrin and other organochlorine insecticides in a plant in the Netherlands. Lengths of exposure were 4-13.2 years. No cases of cancer attributable to pesticide exposure were found.

4.2. BIOASSAYS

4.2.1. Oral. Several long-term studies in which endrin was administered orally to animals were summarized in Table 3-2.

The first study of endrin carcinogenicity was conducted by Treon et al. (1955). Endrin was administered to 28-day-old rats, 20 males and 20 females/group, in doses of 0, 1, 5, 25, 50 or 100 ppm endrin in the feed for 106 weeks. Doses $\geq$25 ppm for females and $\geq$50 ppm for males resulted in significant mortality by 106 weeks so that few animals remained at these higher doses for pathological examination. The authors reported that the incidence of neoplasia was no greater among experimental animals than among controls in the tissues studied (liver, kidney, brain, heart, adrenal gland, spleen, skin, lung and other unidentified tissues). No primary data were presented. Subsequent independent assessment of histological specimens led to the report (Reuber, 1979) that one animal ingesting 25 ppm had a carcinoma of the pituitary and one ingesting 50 ppm a bronchogenic carcinoma.

No malignancies were originally reported in untreated rats although these (and endrin-treated animals) were later reported to have developed benign tumors of the breast and reticulum sarcomas.

Deichmann et al. (1970) fed diets containing 0, 2, 6 or 12 ppm endrin to groups of 50 male and 50 female Osborne-Mendel rats. Male animals treated with 2, 6 or 12 ppm showed 15, 9 and 24 incidences, respectively, of malignant tumors compared with 18% in controls. In females the corresponding incidence of malignancies were 21, 11 and 22% with 24% in control animals. The predominant tumor type in both sexes for all groups was malignant lymphoma. The authors concluded that endrin fed for a lifetime to albino rats was neither tumorigenic nor carcinogenic.

NCI (1979) conducted chronic bioassays with Osborne-Mendel rats and B6C3F1 mice (50/sex/group). Matched controls consisted of 10 rats or mice of each sex. Pooled controls that were used for statistical evaluations consisted of matched controls plus 40 untreated male and 40 untreated female rats or 50 untreated male and 50 untreated female mice from similar studies of other chemicals. Dietary levels were 2.5 or 5 ppm for male rats, 3 or 6 ppm for female rats, 1.6 or 3.2 ppm for male mice and 2.5 or 5 ppm for female mice. Rats were exposed for 80 weeks and sacrificed at 111-114 weeks. Extensive histopathology was conducted of all the major organs in the rats. Comparing incidences of malignant tumor formation in individual tissues between control and treated animals, the authors concluded that endrin was not carcinogenic in either sex of rat. Mice wre exposed for 80 weeks and all surviving mice were sacrificed after 90 or 91 weeks. Because of the high mortality in the treated groups, histological examination of tissue was limited to the liver only. However, a significant incidence of tumors was not observed for any site in either sex. NCI (1979) concluded that under the conditions of this bioassay endrin was not carcinogenic for B6C3F1 mice.

In a lifetime study described by Reuber (1978), groups of 24 male and 24 female 22-day-old Osborne-Mendel rats were fed diets containing 0, 0.1, 1, 5, 10 or 25 ppm endrin. Because 50% of the rats at 25 ppm died within the first week, this group was restarted with 32-day-old rats. Survival did not appear to be affected by treatment. The highest incidence of malignant tumors in male and female rats occurred at 0.1 ppm, but the malignancies were not dose-related. Treated male rats had a higher incidence of renal disease than controls, but this was not dose-related, and the threshold for this effect appeared to be 1 ppm.

Reuber (1979) reviewed two unpublished studies on mice. In one study, a group of 50 male and 50 female C3HF mice were fed a diet containing 2.5 ppm endrin, while a control group of 75 males and 75 females were fed a normal diet for 104 weeks. The 2.5 ppm level was apparently toxic to these mice, causing decreased survival compared with controls. This study was determined to be inadequate for assessing carcinogenicity. In the second mouse study, groups of 100 C57Bl/6J or C3D2F1/J strain mice were fed diets containing 0, 0.3 or 3 ppm endrin. A few mice at the highest dose level initially had convulsions but recovered. Treated female mice had an increased incidence of liver carcinomas, which developed earlier than in controls, but these results are of questionable significance because the high tumor incidence normally seen in untreated mice makes these strains unsuitable for carcinogenicity testing (Reuber, 1979). Furthermore, no dose-related trends in tumor incidence were apparent.

On the basis of these and other studies, Reuber (1979) concluded that endrin was carcinogenic in rats and probably in mice and dogs; however, the absence of a dose-related trend in incidence of any type of tumor in these studies or in the Deichmann et al. (1970) or Treon et al. (1955) studies makes this conclusion questionable.

Reuber (1979) also examined data from the NCI (1979) bioassay using rats. By combining the incidence of benign and malignant tumors or by combining the incidence of carcinomas and sarcomas regardless of site of origin, Reuber (1979) concluded that endrin was carcinogenic in rats and that female rats appeared to be more susceptible than male rats at various target sites. The U.S. EPA (1979b) noted that tumor incidence data reported by Reuber (1979) was subject to interpretation since two other pathologists did not concur with his analysis. U.S. EPA (1979b) concluded that endrin is "unlikely to be a human carcinogen." In reviewing the Reuber (1979) results, the U.S. EPA (1985a) noted that his criteria for assessing carcinogenicity are different from other investigators, and therefore until those differences are resolved it is difficult to draw any conclusions from his findings.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of endrin in experimental animals by inhalation exposure could not be located in the available literature.

4.3. OTHER RELEVANT DATA

U.S. EPA (1985a) reviewed the available data concerning mutagenicity of endrin in various assay systems, and found that endrin generally gave negative results in microbial systems with or without metabolic activation in Drosophila, and in in vitro mammalian systems. A positive result was reported by Dikshith and Datta (1973) who found that intratesticular injections of 0.25 mg endrin caused chromosomal aberrations in germinal tissue of rats.

4.4. WEIGHT OF EVIDENCE

According to U.S. EPA (1986), endrin is most appropriately classified as a Group E chemical, i.e., chemicals for which there is no evidence of carcinogenicity for humans. This classification is based on the negative results from four animal studies including the NCI (1979) bioassay. Endrin has not been classified by IARC (1979); however, the U.S. EPA (1985c) has also reported a Group E classification for endrin.

5. REGULATORY STANDARDS AND CRITERIA

The U.S. EPA (1980a, 1985b) has recommended several criteria for endrin. U.S. EPA (1980a) derived an RfD of 0.001 mg/kg/day based on a rat and dog NOEL of 1 ppm in the diet from the Treon et al. (1955) studies. Using this RfD, U.S. EPA (1980a) derived a water quality criterion of 2.5 µg/ℓ for the protection of human health; however, U.S. EPA (1980a) decided to recommend 1 µg/ℓ as the ambient water criterion to be consistent with the existing drinking water standard of 1 µg/ℓ.

U.S. EPA (1985a,c) derived a RfD of 0.0016 mg/ℓ based the dog dietary NOEL of 1 ppm (0.045 mg/kg/day) reported by Treon et al. (1955). U.S. EPA (1985a) used the dose of 0.2 mg/kg/day from the Revzin (1968) study to calculate 1-day HAs of 0.070 and 0.020 mg/ℓ for adults and children, respectively. U.S. EPA (1985a) used the level of 1 ppm endrin in the diet, equivalent to 0.05 mg/kg/day from the Nelson et al. (1956) study, to calculate 10-day HAs of 0.018 and 0.005 mg/ℓ for adults and children, respectively.

U.S. EPA (1985b) has recommended an RfD of 0.0002 mg/kg/day which is based on a dog NOEL of 0.02 mg/kg/day. ACGIH (1986) recommended a TLV-TWA of 0.1 mg/m³ for occupational atmospheric exposure to endrin, which is the same as the OSHA (1983) standard.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Although the carcinogenicity of endrin is questionable (see Chapter 4), the U.S. EPA (1985a,c) has not performed a quantitative carcinogenicity risk assessment for endrin. U.S. EPA (1979b) concluded that endrin is "unlikely to be a human carcinogen." Therefore, it is appropriate to derive RfD_{SO} and RfD_O values.

The 18-month dog study by Treon et al. (1955) provides the most appropriate basis for an RfD_{SO}. In this study, growth of beagle dogs was affected at 4 ppm endrin in the diet, and dogs fed 3 ppm (0.12-0.25 mg/kg/day) experienced increased relative kidney and heart weights. No adverse effects were observed in four dogs receiving 1 ppm (0.045-0.120 mg/kg/day). Since U.S. EPA (1985a) used the lower end of this range to derive an AADI, the same procedure will be used to derive an RfD_{SO}. Therefore, dividing the NOEL of 0.045 mg/kg/day by an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variations in sensitivity results in an RfD_{SO} of 0.00045 mg/kg/day, or 0.03 mg/day for a 70 kg human. The CBI files contain no data to dispute this RfD_{SO}.

6.1.2. Inhalation (RfD_{SI}). The available data are inadequate for calculation of an RfD_{SI} value for inhalation exposure.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). A review of the literature, including an unpublished study from the CBI files concerning endrin and the various RfD values that have been promulgated by the different branches of the Agency, has indicated that the CBI is the most appropriate basis for an RfD. In this 2-year dog study, beagle dogs (7/sex/group) received diets containing 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm endrin for >2 years. Interim sacrifices (2

dogs/sex/group) were performed at 6 and 12 months. Parameters monitored included growth, food consumption, behavior, serum and urine chemistry, organ weights and histopathology of all major organs. Animals treated at the 2 and 4 ppm dose levels experienced convulsions, slight increase in relative liver weights, and mild histopathological changes in liver cells. Because of the effects observed in the dogs consuming diets containing 2 ppm endrin (0.05 mg/kg/day), this level was considered the LOAEL. No adverse effects were observed in dogs receiving diets containing $\leq$1 ppm endrin. Therefore, 1 ppm (0.025 mg/kg/day) was considered the NOEL. An uncertainty factor of 100 was applied to this NOEL to derive an RfD_0 of 0.00025 mg/kg/day. No uncertainty factor for use of subchronic data was applied in this case because several chronic studies also indicated thresholds near this level. Therefore, the RfD_0 of 0.00025 mg/kg/day is recommended. This value is equivalent to 0.02 mg/day for a 70 kg human.

There is a large amount of long-term oral toxicity data available for endrin that can be used to calculate CSs. Effects associated with chronic oral exposure to endrin include CNS signs, decreased survival, altered organ weights and minor histopathological alteration, and developmental toxicity. Treon et al. (1955) reported decreased survival in rats fed diets containing 50 ppm endrin for 2 years. Decreased survival in mice was observed in a 2-year study by Reuber (1979) at 2.5 ppm in the diet and by NCI (1979) at 3.2 ppm in the diet for 80 weeks. Mice are clearly more sensitive than rats to the life-shortening effects of endrin. Although altered organ weights and minor histopathological lesions were observed in rats at 2 ppm in the diet (Deichmann et al., 1970) and dogs at 1 ppm (Reuber, 1979), the RV_e associated with these effects is not sufficient to generate CSs greater than those associated with reduced survival in mice at slightly higher doses.

Similarly, CNS signs such as hyperexcitability and tremors observed in rats at 2.5 ppm in the diet and in mice at 1.6 ppm (NCI, 1979), if assigned an RV_e of 7, would not be associated with a CS greater than those associated with reduced survival. The CBI files contained a 3-generation reproduction study in rats in which 3 ppm endrin in the diet resulted in increased mortality in the F_{2a} and F_{3a} generations. Table 6-1 contains CSs derived for decreased survival in mice. CNS signs in mice and decreased survival in rats in a 3-generation reproductive study. The maximum CS was obtained using data provided by Reuber (1979) which showed decreased survival in C3HF mice fed 2.5 ppm endrin in the diet for 2 years. These data resulted in a CS of 52 (see Table 6-1).

6.2.2. Inhalation (RfD_I). The only available long-term inhalat were provided by Treon et al. (1955); however, only one concentration was used (~5.4 mg/m³), and this was lethal to some of the mice and rabbits tested. Therefore, no RfD_I can be calculated. It is possible to calculate a CS, however, and this is presented in Table 6-1.

TABLE 6-1

Composite Scores for the Toxicity of Endrin

Species/ Strain/Sex	Exposure/Route/ Dosage	Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	Reference
Mice/C3HF/ M,F	2.5 ppm in diet for 2 years (0.325 mg/kg/day)	1.7[b]	5.2	Decreased survival	10	52	Reuber, 1979
Mice/B6C3F1/ M,F	1.6 ppm in diet for 80 weeks (0.208 mg/kg/day)	1.1[b]	5.5	CNS signs: tremors	7	38.5	NCI, 1979
Rats/Long-Evans/M,F	3 ppm diet for 3 generations (0.15 mg/kg/day)	1.8[c]	5.1	Decreased survival in 3-generation reproductive study	10	51	CBI, 1986
Mice/NR/M,F	5.44 mg/m³ inhalation, 7 hours/day, 130/185 days (1.4 mg/kg/day)[d]	7.4[b]	4.2	Death	10	42	Treon et al., 1955

[a]Human MED is calculated by applying a correction factor to the cube root of the ratio of the body weight of the experimental animal to the reference human body weight of 70 kg, and multiplying the result by 70 kg to express the MED in terms of mg/day for a 70 kg human.

[b]Assumed reference body weight for mice of 0.03 kg (U.S. EPA, 1980c).

[c]Assumed reference body weight for rats of 0.35 kg (U.S. EPA, 1980c).

[d]Equivalent dose expressed as mg/kg/day, estimated by expanding to continuous exposure and assuming values for mice of 0.03 kg body weight and 0.039 m³/day inhalation rate.

NR = Not reported

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APPENDIX

Summary Table for Endrin

	Species	Experimental Exposure/Dose	Effect	Reference Dose (RfD)	Reference
Oral					
RfD_{SQ} (formerly AIS)	dog	1 ppm diet for 18 months (0.045 mg/kg/day)	NOEL for increased relative organ weights	0.03 mg/day	Treon et al., 1955
RfD_{Q} (formerly AIC)	dog	1 ppm diet for 2 years (0.025 mg/kg/day)	NOEL for mild histo-pathological effects in the liver	0.02 mg/day	CBI, 1986
Maximum CS	mice	2.5 ppm diet for 2 years (0.325 mg/kg/day) (RV_d=5.2)	Decreased survival (RV_e=10)	RV_d=1.715 CS=52	Reuber, 1979

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